PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/007530	08.07.2004	08.07.2003

International Patent Classification (IPC) or both national classification and IPC
C12N5/06

Applicant
AXIOGENESIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/007530

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 31-41

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 31-41

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/007530

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-30 and 42-44 in parts

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-30, 42-44
	No:	Claims	1-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	8-30, 42-44
Industrial applicability (IA)	Yes:	Claims	1-30, 42-44
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following documents (D) are referred to in this communication:

D1: WO 01 62899 A (WISCONSIN ALUMNI RES FOUND) 30 August 2001.
D2: US 2003/119107 A1 (DANG STEPHEN ET AL) 26 June 2003.

Introduction

The gist of the present application appears to be the production of embryoid bodies (EBs) from pluriopotent cells, where a high concentration liquid suspension cell culture is agitated until formation of aggregates.

Re Item IV

Lack of Unity of Invention, Rule 13.1, PCT

The IPEA agrees with the objection put forward by the ISA as to lack of unity. The separate inventions are:

Problem 1:	Efficient and cost effective method to produce EBs.
Solution 1:	Methods according to claims 1-30 and use of said method for biological test assays.
Problem 2:	Provision of differentiated cells from multi- or pluripotent cells.
Solution 2:	Embryoid bodies.
Solution 3:	Differentiated cells from EBs.
Problem 3:	Determination of toxicity.
Solution 4:	Biological test of compounds with embryoid bodies.
Problem 4	Provision of biological test methods.
Solution 5:	Use of EBs for loss of function assays.
Solution 6:	Use of EBs for gain of function assays.
Solution 7:	Use of EBs for developmental analysis of teratogenic/embryotoxic compounds.
Solution 8:	Use of EBs for pharmacological assays.
Solution 9:	Use of EBs for microarray systems.

Solution 10: Use of EBs for establishment of model systems for pathological cell functions.

Solution 11: Use of EBs for application of differentiation factors for induction of selectively differentiated cells.

Solution 12: Use of EBs as a source for tissue grafts.

Solution 13: Use of the cell or tissue of claim 32 or 33 for loss of function assays.

Solution 14: Use of the cell or tissue of claim 32 or 33 for gain of function assays.

Solution 15: Use of the cell or tissue of claim 32 or 33 for developmental analysis of teratogenic/embryotoxic compounds.

Solution 16: Use of the cell or tissue of claim 32 or 33 for pharmacological assays.

Solution 17: Use of the cell or tissue of claim 32 or 33 for microarray systems.

Solution 18: Use of the cell or tissue of claim 32 or 33 for establishment of model systems for pathological cell functions.

Solution 19: Use of the cell or tissue of claim 32 or 33 for application of differentiation factors for induction of selectively differentiated cells.

Solution 20: Use of the cell or tissue of claim 32 or 33 as a source for tissue grafts.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty, Art.33(1) and (2), PCT

The present application does not meet the requirements of Novelty, Art.33(1) and (2), PCT, because the subject-matter of claims 1-7 is not new. Attention is drawn to document D1 in which the importance of controlling cell aggregation during formation of EBs from ES cells is disclosed (see paragraph 0054). A cell concentration of 10^6 cells/ml (paragraph 0050) and agitation of the culture system (paragraph 0053) are specifically disclosed.

2. Inventive Step, Art.33(1) and (3), PCT

Claims 8-30 and 42-44 refer to standard culture conditions, standard cell differentiation protocols, and kits the composition of which is simply based on said methods. Said claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or inventive step.

3. Industrial Applicability, Art.33 (1) and (4), PCT

Subject-matter of the present application appears to be industrially applicable under Art.33(1) and (4), PCT.

Re Item VII

Certain defects in the international application

Disclosure of the Invention, Art.5, PCT

1. Independent claim 1 of the present application refers to the production of EBs from multi- or pluriopotent cells, including ES cells, EG cells, or adult stem cells, without further defining the species said cells are derived from. It is implied that agitation of a liquid culture as referred to in claim 1 and demonstrated for mouse ES cells in examples 1-2 has the same effect on all multi- or pluriopotent cells. In this respect applicant's attention is drawn to D1, page 3 which indicates that conventional murine culture protocols fail e.g. for primate cells. Consequently, only the formation of EBs from murine ES cells, as shown in examples 1 and 2 is considered to be sufficiently disclosed under Art.5, PCT.

2. It is pointed out to the applicant that upon entry into the regional phase certain subject-matter claimed in the present application is not patentable. The EPO, for example, does not does not recognize as patentable subject-matter relating to the use of human embryos for commercial purposes.

Re Item VIII

Certain observations on the international application

Clarity of the Claims, Art. 6, PCT

Claim 17 defines the invention by the result to be achieved and is thus not permissible under Art.6, PCT. The wording of the claim simply refers to the underlying technical problem, namely conditions allowing differentiation of the cells into at least one cell type. Said conditions can clearly be defined in other terms without unduly restricting the scope of the claims.

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C. Friedrich